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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/736,801	12/16/2003	Bert Klebl	DEAV2002/0089 US NP	4154

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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	

NOTIFICATION DATE	DELIVERY MODE
12/11/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/736,801	KLEBL ET AL.	
	Examiner	Art Unit	
	JOANNE HAMA	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Non-Final Action of March 19, 2009 on August 18, 2009. Claims 1-23 are cancelled. Claims 24-37 are new.

Claims 24-37, drawn to a method of making a genetically modified yeast, are under consideration.

Withdrawn Rejections

35 USC § 112, 2nd parag.

Applicant's arguments, see page 6 of Applicant's response, filed August 18, 2009, with respect to the rejection of claims 1, 5-7, 9,10, 13-15, 17, 20, 21 as being indefinite have been fully considered and are persuasive. Applicant has cancelled these claims. The rejection of claims 1, 5-7, 9, 10, 13-15, 17, 20, 21 has been withdrawn.

35 USC § 103

Applicant's arguments, see page 10-12 of Applicant's response, filed August 18, 2009, with respect to the rejection of claims 1, 5-7, 13 as being unpatentable over Chattopadhyay et al., 2000 in view of Sauer, 1987 have been fully considered and are persuasive. Applicant indicates that the claims are cancelled. Applicant also indicates that claim 24 is drawn to yeast that has a phenotype that expresses a heterologous protein or protein fragment, which is not taught in Chattopadhyay et al. or Sauer (Applicant's response, page 14). The rejection of claims 1, 5-7, 13 has been withdrawn.

Applicant's arguments, see page 13-16 of Applicant's response, filed August 18, 2009, with respect to the rejection of claims 1, 9, 10, 14, 15, 17-21 as being unpatentable over DeRisi et al., 2000 have been fully considered and are persuasive. Applicant indicates that the claims are cancelled. Applicant also indicates that claim 24 is drawn to yeast that expresses a heterologous protein or protein fragment, which is not taught in DeRisi et al. as DeRisi et al. teach endogenous genes (Applicant's emphasis, Applicant's response, page 14). The rejection of claims 1, 9, 10, 14, 15, 17-21 has been withdrawn.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

New claims 28, 29 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 is drawn to a genetic modification that is a knock out. However, claim 26, upon which claim 28 depends, has already defined the genetic modification to be an expression vector. It is unclear whether claim 28 is meant to be read that the genetic modification further comprises a knock out, or if claim 28 should have depended on claim 26. Claim 29 is included in the rejection because it depends on claim 28.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

New claims 35-37 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Chattopadhyay et al., 2000, Journal of Bacteriology, 182: 6418-6423, previously cited, for reasons of record, April 10, 2007, January 4, 2008, August 12, 2008, March 19, 2009.

Applicant's arguments, see page 6-10 of Applicant's response, filed August 18, 2009, with respect to the rejection of claims 1, 9, 10, 17, 18, 20, 21 as being anticipated by Chattopadhyay et al., 2000 have been fully considered and are persuasive in part.

With regard to claims 1, 9, 10, 17, 18, 20, 21, Applicant indicates that the claims are cancelled. As such, the rejection as it applies to these claims is withdrawn.

With regard to claims 35-37, Chattopadhyay et al. meet the structural limitations of the claimed yeast of claim 35. With regard to claims 36 and 37, an artisan would have want to test substances on Chattopadhyay et al.'s triple mutant yeast in order to find substance that can be used to treat Batten disease.

Thus, the claims are rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

New claims 24-31, 34-37 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Srinivasan et al., 2000, The Journal of Biological Chemistry, 275: 29187-29192, Wilson et al., 1999, PNAS, USA, 96: 12833-12838, Sauer et al., 1987, Molecular and Cellular Biology, 7: 2087-2096, previously cited, Buchholz et al., 1998, Nature Biotechnology, 16: 657-662.

Srinivasan et al. teach that yeast lacking the CuZn-superoxide dismutase (CuZn-SOD) gene (sod1Δ), Mn-SOD (sod2Δ), and sod1Δ/sod2Δ double mutants exhibited elevated levels of iron throughout their growth, but particularly in the stationary phase (Srinivasan et al., abstract).

While Srinivasan et al. teach single and double mutants of SOD, they do not teach that sod1Δ or sod2Δ single mutants were further genetically engineered with a transgene construct that conditionally disrupted sod2 or sod1, such that double mutants of sod could be obtained and studied. An artisan would have wanted to study the effects of a second sod mutation in yeast because double mutant yeast has a more severe phenotype than the single mutant (Srinivasan et al., 29187, 2nd col., 1st parag.). One way of studying the effects of a second sod mutation on sod single mutation yeast is via microarrays, wherein samples of yeast are characterized over a number of time points. Illustrating this concept, Wilson et al. teach that microarrays were used to study

the changes in gene expression of tuberculosis following drug treatment. With regard to making an inducible knockout, Sauer teaches that the cre-lox site-specific recombination system was shown to function in an efficient manner in yeast. The cre gene, which codes for a site-specific recombinase, was placed under control of the yeast GAL1 promoter. lox sites flanking the LEU2 gene were integrated into two different chromosomes in both orientations. Excisive recombination at the lox sites (as measured by the loss of the LEU2 gene) was promoted efficiently by the Cre protein and was dependent upon induction by galactose (Sauer, abstract).

With regard to the claims being drawn to screening the yeast for substances that affect the function of a heterologous expressed protein or protein fragment (claims 36, 37), Buchholz et al. teach that artisans were actively looking for cre recombinases that had better enzymatic properties (Buchholz et al., abstract). While Buchholz et al. teach one method of mutating the sequence of a recombinase, an artisan would have also screened for substances that affect the activity of cre recombinase.

Thus, the claims are rejected.

New claims 24-26, 30-37 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over DeRisi et al., 2000, FEBS Letters, 470: 156-160, previously cited, Gari et al., 1997, Yeast, 13: 837-848, Wilson et al., 1999, PNAS, USA, 96: 12833-12838.

As indicated in the Office Action of March 19, 2009, DeRisi et al. teach that Pdr1p/Pdr3p transcription factors render the cell resistant to chemical and nutritional

stress in several ways other than the well-known regulation of ABC efflux transporters. After overexpressing Pdr1p and/or Pdr3p in S. cerevisiae and identifying upregulated and downregulated genes, DeRisi et al. teach that many of the genes overexpressed by the PDR1-3 and PDR3-7 mutations encode proteins that reduce intracellular accumulation of hydrophobic compounds, modulate enzymes involved in lipid synthesis and cell wall metabolism. DeRisi et al. teach that it would be interesting to investigate whether similar strategies for defense against noxious chemical agents are employed by other microorganisms, such as pathogenic yeasts (DeRisi et al., abstract and page 159, 2nd col., 3rd parag.).

While DeRisi et al. do not specifically teach that the upregulated genes in yeast overexpressing Pdr1p and/or Pdr3p were knocked out or that the downregulated genes were overexpressed, it would have been obvious for an artisan to knockout the upregulated genes and overexpress the downregulated genes in Pdr1p, Pdr3p or Pdr1p/Pdr3p yeast, such that an artisan would eliminate yeast that are resistant to chemical and nutritional stress. An artisan would have carried out the method in S. cerevisiae and adapted the treatment to pathogenic yeast.

With regard to the claims being drawn to the yeast expressing a heterologous gene (claim 24), in the case where overexpression of Pdr1p, Pdr3p or Pdr1p/Pdr3p results in downregulation of a gene, that gene can be overexpressed under an inducible system to see what effect(s) gene overexpression has on yeast survival. At the time of filing, Gari et al. teach the tetracycline-regulatable promoter system, wherein tetracycline induces tetO-driven gene expression and induces expression of a gene of

interest (Gari et al., page 838, 1st col., 3rd parag.). Time course studies of mRNA expression patterns following induction were known at the time of filing. For example, see Wilson et al., who teach changes in gene expression following treatment with a drug. One would have made a Pdr1p, Pdr3p, or Pdr1/Pdr3p overexpression line, placed a gene of interest that is downregulated when Pdr1p, Pdr3p or Pdr1p/Pdr3p is overexpressed under the control of the tetracycline system, split the yeast in half and induced on half with tetracycline, in order to determine what effect(s) overexpression of the compensating gene has on yeast.

With regard to the claims being drawn to the yeast not exhibiting a detectable change in phenotype (claim 24), the yeast taught by DeRisi et al. do not have a detectable phenotype as the morphology of the yeast is unaffected. In addition to this, DeRisi et al. can be interpreted to exhibit no detectable phenotype on the behavior of the organism when the detectable phenotype is defined to be rate of proliferation. However, the rate of proliferation would be affected in Pdr1p and/or Pdr3p yeast that comprise a deletion in an upregulated gene or in yeast that comprise a construct overexpressing a downregulated gene as the upregulated genes are drawn to genes involved in drug resistance (DeRisi et al., page 158) and genes that are downregulated are drawn to genes involved in transport of acids (DeRisi et al., page 159), which would affect the homeostasis of the yeast.

With regard to the claims being drawn to using the yeast in screens (claims 36, 37), given that DeRisi et al. teach that overexpression of Pdr1p and/or Pdr3p results in drug-resistant yeast, an artisan would have wanted to use the yeast to screen for

compounds that affect Pdr1p and/or Pdr3p, such that compounds can be identified to treat patients with pathogenic yeast.

Thus, the claims are rejected.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Mondays, Tuesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Joanne Hama/
Primary Examiner
Art Unit 1632